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Areas of Interest: **Endocrinology of breast cancer; endocrine disruption**

OVERALL AIMS are to study the cellular and molecular basis of action of oestrogen and oestrogen-mimicking compounds on the development, growth and progression of breast cancer cells. Research is focused in two major areas as detailed below.

ENDOCRINE RESISTANCE OF BREAST CANCER: Clinical, experimental and epidemiological studies leave no doubt that oestrogen plays a major role in breast cancer and blockade of oestrogen action can be used as a successful therapeutic strategy to inhibit tumour growth. However, endocrine therapy is invaribly limited by the ability of the cancer cells to escape from growth inhibition imposed through oestrogen deprivation and to grow independently of oestrogen. I have developed human breast cancer cell culture models to investigate molecular mechanisms, and studies are currently focused on finding new ways of inhibiting the oestrogen-independent cells which might have therapeutic benefit.

ENDOCRINE DISRUPTION AND BREAST CANCER: The central role of oestrogen in breast cancer poses serious unanswered questions concerning the role of the many environmental chemicals which possess oestrogenic activity and which can enter the human breast. In the modern world, the breast is exposed to numerous oestrogenic compounds through diet, the domestic environment and use of cosmetic products. Studies are focused on determining the cellular and molecular actions of oestrogenic compounds which can be measured in the human breast and on trying to understand how exposure to multiple compounds in the long-term may impact on breast biology. If exposure to complex mixtures of oestrogenic chemicals is a factor in breast cancer development, then a strategy for prevention of breast cancer might become a reality.

J Appl Toxicol. 2013 Jan 31. doi: 10.1002/jat.2850. [Epub ahead of print]

Combinations of parabens at concentrations measured in human breast tissue can increase proliferation of MCF-7 human breast cancer cells.

Charles AK, Darbre PD.

Source

School of Biological Sciences, University of Reading, Reading, RG66UB, UK.

Abstract

The alkyl esters of p-hydroxybenzoic acid (parabens), which are used as preservatives in consumer products, possess oestrogenic activity and have been measured in human breast tissue. This has raised concerns for a potential involvement in the development of human breast cancer. In this paper, we have investigated the extent to which proliferation of MCF-7 human breast cancer cells can be increased by exposure to the five parabens either alone or in combination at concentrations as recently measured in 160 human breast tissue samples. Determination of no-observed-effect concentrations (NOEC), lowest-observed-effect concentrations (LOEC), EC(50) and EC(100) values for stimulation of proliferation of MCF-7 cells by five parabens revealed that 43/160 (27%) of the human breast tissue samples contained at least one paraben at a concentration ≥ LOEC and 64/160 (40%) > NOEC. Proliferation of MCF-7 cells could be increased by combining all five parabens at concentrations down to the 50(th) percentile (median) values measured in the tissues. For the 22 tissue samples taken at the site of ER+ PR+ primary cancers, 12 contained a sufficient concentration of one or more paraben to stimulate proliferation of MCF-7 cells. This demonstrates that parabens, either alone or in combination, are present in human breast tissue at concentrations sufficient to stimulate the proliferation of MCF-7 cells in vitro, and that functional consequences of the presence of paraben in human breast tissue should be assessed on the basis of all five parabens and not single parabens individually.

J Epidemiol Community Health. 2013 Mar;67(3):203-5. doi: 10.1136/jech-2012-201362. Epub 2012 Oct 30.

Environmental oestrogens and breast cancer: long-term low-dose effects of mixtures of various chemical combinations.

Darbre PD, Fernandez MF.

Source

Biomedical Sciences Section, School of Biological Sciences, Hopkins Building, University of Reading, Whiteknights, Reading RG6 6UB, UK; p.d.darbre@reading.ac.uk.

PMID: 23112279 [PubMed - in process]

The incidence of breast cancer has risen worldwide to unprecedented levels in recent decades, making it now the major cancer of women in many parts of the world.1 Although diet, alcohol, radiation and inherited loss of BRCA1/2 genes have all been associated with increased incidence, the main identified risk factors are life exposure to hormones including physiological variations associated with puberty/pregnancy/menopause,1 personal choice of use of hormonal contraceptives2 and/or hormone replacement therapy.3–6 On this basis, exposure of the human breast to the many environmental pollutant chemicals capable of mimicking or interfering with oestrogen action7 should also be of concern.8 Hundreds of such environmental chemicals have now been measured in human breast tissue from a range of dietary and domestic exposure sources7 9 including persistent organochlorine pollutants...

J Appl Toxicol. 2012 Jun 29. doi: 10.1002/jat.2753. [Epub ahead of print]

Parabens enable suspension growth of MCF-10A immortalized, non-transformed human breast epithelial cells.

Khanna S, Darbre PD.

Source

Biomedical Sciences Section, School of Biological Sciences, University of Reading, Reading, RG6 6UB, UK.

Abstract

Parabens (alkyl esters of p-hydroxybenzoic acid) are used extensively as preservatives in consumer products, and intact esters have been measured in several human tissues. Concerns of a potential link between parabens and breast cancer have been raised, but mechanistic studies have centred on their oestrogenic activity and little attention has been paid to any carcinogenic properties. In the present study, we report that parabens can induce anchorage-independent growth of MCF-10A immortalized but non-transformed human breast epithelial cells, a property closely related to transformation and a predictor of tumour growth in vivo. In semi-solid methocel suspension culture, MCF-10A cells produced very few colonies and only of a small size but the addition of 5 × 10(-4) M methylparaben, 10(-5) M n-propylparaben or 10(-5) M n-butylparaben resulted in a greater number of colonies per dish ($P < 0.05$ in each case) and an increased average colony size ($P < 0.001$ in each case). Dose-responses showed that concentrations as low as 10(-6) M methylparaben, 10(-7) M n-propylparaben and 10(-7) M n-butylparaben could increase colony numbers ($P = 0.016$, $P = 0.010$, $P = 0.008$, respectively): comparison with a recent measurement of paraben concentrations in human breast tissue samples from 40 mastectomies (Barr et al., 2012) showed that 22/40 of the patients had at least one of the parabens at the site of the primary tumour at or above these concentrations. To our knowledge, this is the first study to report that parabens can induce a transformed phenotype in human breast epithelial cells in vitro, and further investigation is now justified into a potential link between parabens and breast carcinogenesis.

J Appl Toxicol. 2012 Mar;32(3):219-32. doi: 10.1002/jat.1786. Epub 2012 Jan 12.

Measurement of paraben concentrations in human breast tissue at serial locations across the breast from axilla to sternum.

Barr L, Metaxas G, Harbach CA, Savoy LA, Darbre PD.

Source

The Genesis Breast Cancer Prevention Centre, University Hospital of South Manchester NHS Foundation Trust, Wythenshawe, Manchester, M23 9LT, UK.

Abstract

The concentrations of five esters of p-hydroxybenzoic acid (parabens) were measured using HPLC-MS/MS at four serial locations across the human breast from axilla to sternum using human breast tissue collected from 40 mastectomies for primary breast cancer in England between 2005 and 2008. One or more paraben esters were quantifiable in 158/160 (99%) of the tissue samples and in 96/160 (60%) all five esters were measured. Variation was notable with respect to individual paraben esters, location within one breast and similar locations in different breasts. Overall median values in nanograms per gram tissue for the 160 tissue samples were highest for n-propylparaben [16.8 (range 0-2052.7)] and methylparaben [16.6 (range 0-5102.9)]; levels were lower for n-butylparaben [5.8 (range 0-95.4)], ethylparaben [3.4 (range 0-499.7)] and isobutylparaben 2.1 (range 0-802.9). The overall median value for total paraben was 85.5 ng g(-1) tissue (range 0-5134.5). The source of the paraben cannot be identified, but paraben was measured in the 7/40 patients who reported never having used underarm cosmetics in their lifetime. No correlations were found between paraben concentrations and age of patient (37-91 years), length of breast feeding (0-23 months), tumour location or tumour oestrogen receptor content. In view of the disproportionate incidence of breast cancer in the upper outer quadrant, paraben concentrations were compared across the four regions of the breast: n-propylparaben was found at significantly higher levels in the axilla than mid (P = 0.004 Wilcoxon matched pairs) or medial (P = 0.021 Wilcoxon matched pairs) regions (P = 0.010 Friedman ANOVA).

J Inorg Biochem. 2011 Nov;105(11):1484-8. doi: 10.1016/j.jinorgbio.2011.07.017. Epub 2011 Jul 31.

Aluminium and human breast diseases.

Darbre PD, Pugazhendhi D, Mannello F.

Source

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Abstract

The human breast is exposed to aluminium from many sources including diet and personal care products, but dermal application of aluminium-based antiperspirant salts provides a local long-term source of exposure. Recent measurements have shown that aluminium is present in both tissue and fat of the human breast but at levels which vary both between breasts and between tissue samples from the same breast. We have recently found increased levels of aluminium in noninvasively collected nipple aspirate fluids taken from breast cancer patients (mean 268 ± 28 μg/l) compared with control healthy subjects (mean 131 ± 10 μg/l) providing evidence of raised aluminium levels in the breast microenvironment when cancer is present. The measurement of higher levels of aluminium in type I human breast cyst fluids (median 150 μg/l) compared with human serum (median 6 μg/l) or human milk (median 25 μg/l) warrants further investigation into any possible role of aluminium in development of this benign breast disease. Emerging evidence for aluminium in several breast structures now requires biomarkers of aluminium action in order to ascertain whether the presence of aluminium has any biological impact. To this end, we report raised levels of proteins that modulate iron homeostasis (ferritin, transferrin) in parallel with raised aluminium in nipple aspirate fluids in vivo, and we report overexpression of mRNA for several S100 calcium binding proteins following long-term exposure of MCF-7 human breast cancer cells in vitro to aluminium chlorhydrate.

J Appl Toxicol. 2011 Apr;31(3):262-9. doi: 10.1002/jat.1641. Epub 2011 Feb 21.

Analysis of aluminium content and iron homeostasis in nipple aspirate fluids from healthy women and breast cancer-affected patients.

Mannello F, Tonti GA, Medda V, Simone P, Darbre PD.

Source

Department of Biomolecular Sciences, Section of Clinical Biochemistry, Unit of Cell Biology, University 'Carlo Bo', via O. Ubaldini 7, 61029, Urbino, Italy.

Abstract

Aluminium is not a physiological component of the breast but has been measured recently in human breast tissues and breast cyst fluids at levels above those found in blood serum or milk. Since the presence of aluminium can lead to iron dyshomeostasis, levels of aluminium and iron-binding proteins (ferritin, transferrin) were measured in nipple aspirate fluid (NAF), a fluid present in the breast duct tree and mirroring the breast microenvironment. NAFs were collected noninvasively from healthy women (NoCancer; n = 16) and breast cancer-affected women (Cancer; n = 19), and compared with levels in serum (n = 15) and milk (n = 45) from healthy subjects. The mean level of aluminium, measured by ICP-mass spectrometry, was significantly higher in Cancer NAF (268.4 ± 28.1 μg l(-1) ; n = 19) than in NoCancer NAF (131.3 ± 9.6 μg l(-1) ; n = 16; $P < 0.0001$). The mean level of ferritin, measured through immunoassay, was also found to be higher in Cancer NAF (280.0 ± 32.3 μg l(-1)) than in NoCancer NAF (55.5 ± 7.2 μg l(-1)), and furthermore, a positive correlation was found between levels of aluminium and ferritin in the Cancer NAF (correlation coefficient $R = 0.94$, $P < 0.001$). These results may suggest a role for raised levels of aluminium and modulation of proteins that regulate iron homeostasis as biomarkers for identification of women at higher risk of developing breast cancer. The reasons for the high levels of aluminium in NAF remain unknown but possibilities include either exposure to aluminium-based antiperspirant salts in the adjacent underarm area and/or preferential accumulation of aluminium by breast tissues.

J Endocrinol. 2011 Jan;208(1):21-9. doi: 10.1677/JOE-10-0137. Epub 2010 Oct 14.

Enhanced sensitivity to rapamycin following long-term oestrogen deprivation in MCF-7, T-47-D and ZR-75-1 human breast cancer cells.

Ray S, Fry MJ, Darbre PD.

Source

Biomedical Sciences Section, School of Biological Sciences, University of Reading, Hopkins Building, Whiteknights, Reading RG6 6UB, UK.

Abstract

Human breast cancer cells (MCF-7, T-47-D and ZR-75-1) can adapt to circumvent any reduced growth rate during long-term oestrogen deprivation, and this provides three model systems to investigate mechanisms of endocrine resistance in breast cancer. In this paper we report consistent differences in the effects of three growth inhibitors following long-term oestrogen deprivation in all three cell models. Long-term oestrogen deprivation of MCF-7, T-47-D and ZR-75-1 cells resulted in reduced growth inhibition by PD98059 (2-10 μg/ml), implying a loss of dependence on mitogen-activated protein kinase pathways for growth. The growth inhibitor LY294002 (2-10 μM) inhibited growth of both oestrogen-maintained and oestrogen-deprived cells with similar dose-responses, implying continued similar dependence on phosphoinositide 3-kinase (PI3K) pathways with no alteration after adaptation to oestrogen independent growth. However, by contrast, long-term oestrogen deprivation resulted in an increased sensitivity to growth inhibition by rapamycin, which was not reduced by readdition of oestradiol. The enhanced inhibition of long-term oestrogen-deprived MCF-7-ED, T-47-D-ED and ZR-75-1-ED cell growth by combining rapamycin with LY294002 at concentrations where each alone had little effect, offers preclinical support to the development of therapeutic combinations of rapamycin analogues with other PI3K inhibitors in endocrine-resistant breast cancer.

PMID: 20947540 [PubMed - indexed for MEDLINE] **Free full text**

Anticancer Res. 2010 Mar;30(3):815-27.

Environmental oestrogens and breast cancer: evidence for combined involvement of dietary, household and cosmetic xenoestrogens.

Darbre PD, Charles AK.

Source

Biomedical Sciences Section, School of Biological Sciences, The Hopkins Building, The University of Reading, Whiteknights, Reading RG6 6UB, UK. p.d.darbre@reading.ac.uk

Abstract

Many environmental compounds with oestrogenic activity are measurable in the human breast and oestrogen is a known factor in breast cancer development. Exposure to environmental oestrogens occurs through diet, household products and cosmetics, but concentrations of single compounds in breast tissue are generally lower than needed for assayable oestrogenic responses. Results presented here and elsewhere demonstrate that in combination, chemicals can give oestrogenic responses at lower concentrations, which suggests that in the breast, low doses of many compounds could sum to give a significant oestrogenic stimulus. Updated incidence figures show a continued disproportionate incidence of breast cancer in Britain in the upper outer quadrant of the breast which is also the region to which multiple cosmetic chemicals are applied.

CONCLUSION: If exposure to complex mixtures of oestrogenic chemicals in consumer products is a factor in breast cancer development, then a strategy for breast cancer prevention could become possible.

PMID: 20393002 [PubMed - indexed for MEDLINE]

Breast Cancer Res. 2009;11 Suppl 3:S5. doi: 10.1186/bcr2424. Epub 2009 Dec 18.

Underarm antiperspirants/deodorants and breast cancer.

Darbre PD.

Source

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PMID: 20030880 [PubMed - indexed for MEDLINE]
PMCID: PMC2797685 Free PMC Article

J Appl Toxicol. 2009 Jul;29(5):422-34. doi: 10.1002/jat.1429.

Oestrogenic activity of benzyl salicylate, benzyl benzoate and butylphenylmethylpropional (Lilial) in MCF7 human breast cancer cells in vitro.

Charles AK, Darbre PD.

Source

University of Reading, UK.

Abstract

Benzyl salicylate, benzyl benzoate and butylphenylmethylpropional (Lilial) are added to bodycare cosmetics used around the human breast. We report here that all three compounds possess oestrogenic activity in assays using the oestrogen-responsive MCF7 human breast cancer cell line. At 3 000 000-fold molar excess, they were able to partially displace [(3)H]oestradiol from recombinant human oestrogen receptors ERalpha and ERbeta, and from cytosolic ER of MCF7 cells. At concentrations in the range of 5 x 10(-5) to 5 x 10(-4)m, they were able to increase the expression of a stably integrated oestrogen-responsive reporter gene (ERE-CAT) and of the endogenous oestrogen-responsive pS2 gene in MCF7 cells, albeit to a lesser extent than with 10(-8)m 17beta-oestradiol. They increased the proliferation of oestrogen-dependent MCF7 cells over 7 days, which could be inhibited by the antioestrogen fulvestrant, suggesting an ER-mediated mechanism. Although the extent of stimulation of proliferation over 7 days was lower with these compounds than with 10(-8)m 17beta-oestradiol, given a longer time period of 35 days the extent of proliferation with 10(-4)m benzyl salicylate, benzyl benzoate or butylphenylmethylpropional increased to the same magnitude as observed with 10(-8)m 17beta-oestradiol over 14 days. This demonstrates that benzyl salicylate, benzyl benzoate and butylphenylmethylpropional are further chemical components of cosmetic products which give oestrogenic responses in a human breast cancer cell line in culture. Further research is now needed to investigate whether oestrogenic responses are detectable using in vivo models and the extent to which these compounds might be absorbed through human skin and might enter human breast tissues.

J Steroid Biochem Mol Biol. 2009 Mar;114(1-2):21-32. doi: 10.1016/j.jsbmb.2008.12.017. Epub 2009 Jan 9.

Use of global gene expression patterns in mechanistic studies of oestrogen action in MCF7 human breast cancer cells.

Sadler AJ, Pugazhendhi D, Darbre PD.

Source

School of Biological Sciences, University of Reading, Whiteknights, Reading RG6 6UB, UK.

Abstract

Over the years, the MCF7 human breast cancer cell line has provided a model system for the study of cellular and molecular mechanisms in oestrogen regulation of cell proliferation and in progression to oestrogen and antioestrogen independent growth. Global gene expression profiling has shown that oestrogen action in MCF7 cells involves the coordinated regulation of hundreds of genes across a wide range of functional groupings and that more genes are downregulated than upregulated. Adaptation to long-term oestrogen deprivation, which results in loss of oestrogen-responsive growth, involves alterations to gene patterns not only at early time points (0-4 weeks) but continuing through to later times (20-55 weeks), and even involves alterations to patterns of oestrogen-regulated gene expression. Only 48% of the genes which were regulated > or =2-fold by oestradiol in oestrogen-responsive cells retained this responsiveness after long-term oestrogen deprivation but other genes developed de novo oestrogen regulation. Long-term exposure to fulvestrant, which resulted in loss of growth inhibition by the antioestrogen, resulted in some very large fold changes in gene expression up to 10,000-fold. Comparison of gene profiles produced by environmental chemicals with oestrogenic properties showed that each ligand gave its own unique expression profile which suggests that environmental oestrogens entering the human breast may give rise to a more complex web of interference in cell function than simply mimicking oestrogen action at inappropriate times.

PMID: 19167489 [PubMed - indexed for MEDLINE]